REMARKS

Applicants thank the Examiner for accepting the previous amendments to claim 44 and acknowledging their support in the application as filed. Applicants also thank the Examiner for accepting the petition to correct inventorship and for forwarding the application to the Office of Initial Patent Examination (OIPE) for issuance of a corrected filing receipt and for correction of the Office records.

Finally, applicants thank the Examiner for reconsidering and withdrawing the § 112 rejections (written description and enablement) of the amended claims.

The Claim Amendments

Claims 44 and 53 are pending. Applicants had previously canceled claims 1-43, 45-52, and 54-62, which are drawn to non-elected inventions.

Applicants have amended claim 44 (and thus dependent claim 53) to recite certain specific embodiments of the invention – a method for the treatment of Mild Cognitive Impairment (MCI). This amendment is fully supported by the specification and does not encompass new matter. In particular, support for the amendment can be found, for example, at paragraphs [0003], [0022, see in particular p. 4 line 6], [0057], and [0125] of the published application (US Publication No. 2004/0191803).

Applicants have made this amendment solely to expedite prosecution of the present application. Applicants reserve the right to prosecute the claims to the canceled subject matter in one or more patent applications claiming benefit to or priority from this application.

Applicants request reconsideration of amended claims 44 and 53.

The Rejections

(1) 35 U.S.C. § 102(e) – Novelty

Claims 44 and 53 stand rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Ohuchida et al., U.S. Patent No. 7,176,240 ("Ohuchida"). The Examiner states that Ohuchida discloses "a method for treatment of neurodegenerative diseases (including Alzheimer's disease) comprising administering pentanoic acid derivatives, including valproic acid," (page 6 of the Office Action), and that "the instant application and [Ohuchida] overlap with respect to the treatment groups and the actual treatment using pentanoic acid derivatives" (page 8 of the Office Action). Applicants traverse this rejection. It is moot in view of the amended claims.

Solely to expedite prosecution, applicants have amended claims 44 and 53 to recite "[a] method of treating Mild Cognitive Impairment (MCI) in a mammal." Ohuchida does not teach the claimed method.

As the Examiner has acknowledged, Ohuchida only relates to the treatment of neurodegenerative diseases (including Alzheimer's disease) (page 6 of the Office Action). Indeed, Ohuchida recites that certain pentanoic acid derivatives "are expected to be useful" in treating neurodegenerative disease attributed to abnormal/reactive astrocytes (see, column 3, lines 7-34, column 31, lines 15-29 of Ohuchida). Indeed, Ohuchida notes that reactive astrocytes elicit a

neurotoxic activity and cause neuronal death and thus, certain pentanoic acid derivatives, which inhibit the activities of reactive astrocytes, may be used to prevent such neurotoxic activity (see, column 2, lines 20-22 and 47-56, and column 3, lines 54-56 of Ohuchida).

Claims 44 and 53, as amended, are directed to a method of treating Mild Cognitive Impairment (MCI). Mild Cognitive Impairment is a diagnosis given to individuals who have cognitive impairments beyond what are expected for their age, but that do not interfere significantly with their daily activities. *See, e.g.*, Petersen R. et al., *Arch. Neurol.* vol, 56 (3): 303-08 (1999) ("Petersen," attached as Exhibit A), at page 304 ("Subjects and Methods," right column). Clinically, Mild Cognitive Impairment is distinguishable from dementia or Alzheimer's Disease and represents a unique group of patients. *See, e.g.*, Grundman. et al., *Arch. Neurol.* vol, 61 (1): 59-66 (2004) ("Grundman," attached as Exhibit B), at page 59 (conclusions) and page 64 (right column). *See also*, Petersen, which reports that patients with MCI are clinically distinguishable from normal subjects and patients with even mild Alzheimer's Disease (pages 303 (conclusions); and page 305, Table, right column). MCI patients may, but do not necessarily, progress to clinically probable Alzheimer's Disease. Indeed, the rate of progression is estimated at about 10% to 15% per year (see, Grundman, page 59, right column). Thus, claims 44 and 53, as amended, are directed to the treatment of a condition (MCI) that is neither taught nor suggested by Ohuchida. Nor does the condition treated in the method of the amended claims overlap with those addressed by Ohuchida.

In addition to being clinically distinct, MCI and Alzheimer's Disease differ pathologically. fMRI studies have shown that MCI subjects and controls (cognitively unimpaired individuals) do not differ in hippocampal or entorhinal volumes. By contrast, patients with Alzheimer's Disease had smaller hippocampal and entorhinal volumes. *See*, Dickerson, B., et al., *Neurology*, vol. 65:

404-411 (2005) ("Dickerson," attached as Exhibit C), at page 407 (right column), and in Figure 4. These data indicate that there is neurodegeneration (atrophy) associated with Alzheimer's Disease but not with MCI (see, Dickerson, Figure 4, legend). Even after correcting for volume, Dickerson reports that hippocampal activation was greater in MCI and diminished in Alzheimer's Disease, as compared to controls (see, Dickerson, at page 409, right column). These activation data likewise confirm that in contrast to Alzheimer's Disease, there is no atrophy or neurodegeneration in MCI subjects (see, Dickerson, at page 409, right column).

The teachings of the instant application are consistent with Petersen, Grundman and Dickerson. MCI and neurodegeneration diseases are clinically and pathologically different, and do not overlap. For example, the instant application reports that age-related cognitive impairment occurs independently of neurodegeneration, such as that involving the loss of neurons or the widespread degradation of relevant circuits (see, paragraph [0008] of the published application). In addition, Examples 9.1.5 and 9.1.9 report the classification of aged, cognitive-impaired rats, using established memory tests such as Morris Water Maze analysis and Radial Arm Maze analysis. The aged, cognitive-impaired rats in Examples 9.1.5 and 9.1.9 suffered from memory loss (as indicated by the memory tests), but did not suffer from neurodegeneration, as evidenced in Rapp, P., et al., *Proc. Natl. Acad. Sci. USA*, vol 93: 9926-9930 ("Rapp," attached as Exhibit D). See also, paragraph [0008] of the published application. Rapp reports that there were comparable numbers of neurons in the young group, aged-unimpaired group, and aged-impaired group (see, e.g., Figures 2 and 3 of Rapp). Finally, the efficacy of valproic acid and sodium valproate in treating Mild Cognitive Impairment has been demonstrated by Koh et al. (submitted by the applicants in the Response filed

November 2, 2007). Thus, the amended claims recite a method of treating a disease (MCI) that is different from Alzheimer's Disease and other neurodegenerative diseases.

Therefore, Ohuchida, which only refers to the treatment of neurodegenerative diseases (i.e., ones caused by reactive astrocytes), fails to teach each and every limitation of the amended claims. Ohuchida never teaches or suggests treating Mild Cognitive Impairment, a condition that is both clinically and physiologically different from neurodegenerative diseases. As such, Ohushida does not anticipate the claims 44 and 53, as amended.

Applicants respectfully request reconsideration and withdrawal of this rejection.

(2) 35 U.S.C. § 112, Second Paragraph

Claims 44 and 53 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Applicants have amended claim 44 to recite the term "a compound having the formula" immediately following the word "of," as the Examiner has suggested. Support for the amendments can be found, for example, in paragraph [0288] of the published application.

Applicants previously amended claim 53 to depend from claim 44 (see, page 3 of the Response filed November 2, 2007). Applicants believe the claim number "44," which may not be easily perceived between the two strike-through marks deleting the prior and subsequent claim numbers, was actually correctly recited in the previous amendment, and no further amendment is necessary.

CONCLUSION

The Examiner is invited to telephone the undersigned to discuss any issue pertaining to this response. Applicants request favorable consideration of the application and early allowance of the

pending claims. If additional fees are due, please charge our **Deposit Account No. 18-1945**, under Order No. JHUC-008-101 from which the undersigned is authorized to draw.

Dated: May 08, 2008

Respectfully submitted,

By _____

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